

Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application. The amendments made herein are made without prejudice or disclaimer.

Listing of Claims:

1-37. (Cancel)

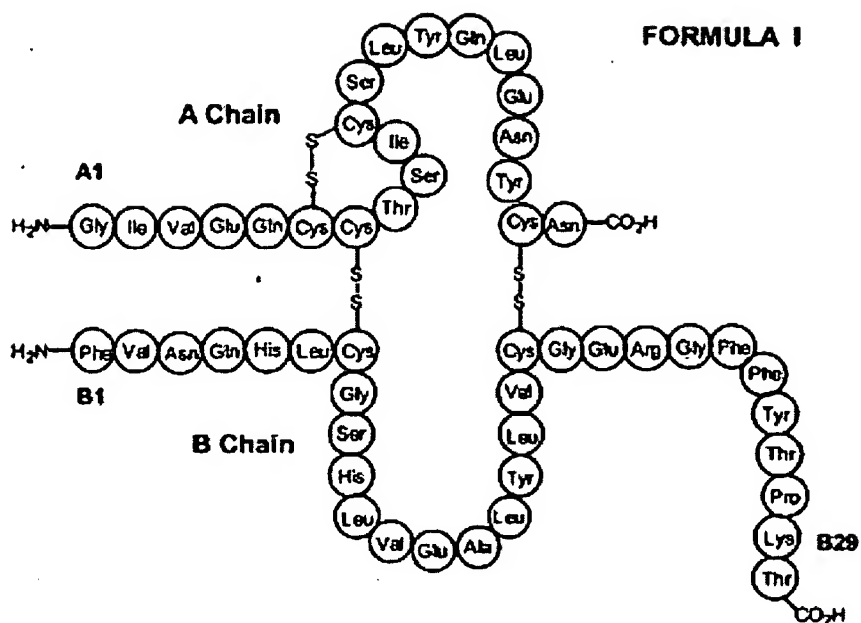
38. (Currently amended) An insulin derivative comprising an insulin molecule and a reactive group for covalently bonding a ~~blood protein~~ albumin, the insulin molecule comprising an A chain and a B chain and the reactive group being a maleimido-containing group, wherein the reactive group is coupled to an ~~available amino group of the insulin molecule selected from the~~ α -amino groups group of the N-terminus amino acids—acid of chains A and the B chain of the insulin molecule and the ϵ -amino group of Lys B29.

39.-40. (Cancel)

41. (Currently amended) The insulin derivative of claim 38, wherein the ~~available amino~~ α -amino group is the α -amino group of Phe B1.

42. (Previously presented) The insulin derivative of claim 38, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

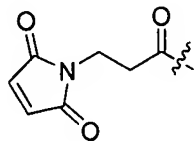
43. (Currently amended) The insulin derivative of claim 38, wherein the insulin molecule is of formula I:



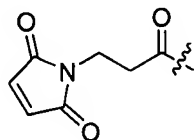
and the reactive group is coupled to an amino acid of the insulin molecule at a position ~~selected from the positions Gly A1, Phe B1 and Lys B29 of the insulin molecule.~~

44. (Cancel)

45. (Currently amended) The insulin derivative of claim 38, wherein the reactive group coupled to the α -amino ~~available-amine~~ group of the insulin molecule is:



46. (Currently amended) The insulin derivative of claim 41, wherein the reactive group coupled to the ~~available-amine~~ α -amino group of the insulin molecule is:



47. (Cancel)

48. (Currently amended) The insulin derivative of claim 38, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

49. (Currently amended) The insulin derivative of claim 41, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

50. (Currently amended) The insulin derivative of claim 46, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

51. (Currently amended) The insulin derivative of claim [[47]] 45, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

52. (Currently amended) The insulin derivative of claim 48, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amino~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

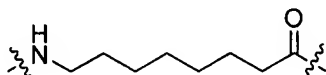
53. (Currently amended) The insulin derivative of claim 49, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amino~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

54. (Currently amended) The insulin derivative of claim 50, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amino~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino)

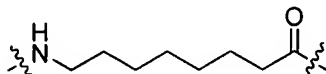
ethoxy)] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

55. (Previously presented) The insulin derivative of claim 51, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy)] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

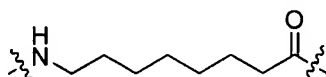
56. (Previously presented) The insulin derivative of claim 48, wherein the linker is:



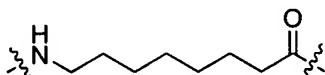
57. (Previously presented) The insulin derivative of claim 49, wherein the linker is:



58. (Previously presented) The insulin derivative of claim 50, wherein the linker is:



59. (Previously presented) The insulin derivative of claim 51, wherein the linker is:



60. (Cancel)

61. (Currently amended) The insulin derivative of claim ~~[[44]]~~ 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

62. (Currently amended) The insulin derivative of claim [[44]] 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropionylcarbonyl)aminooctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropionylcarbonyl)aminooctanamide.

63. (Cancel)

64. (Cancel)

65. (Currently amended) The insulin derivative of claim [[64]] 38, wherein the albumin is recombinant albumin.

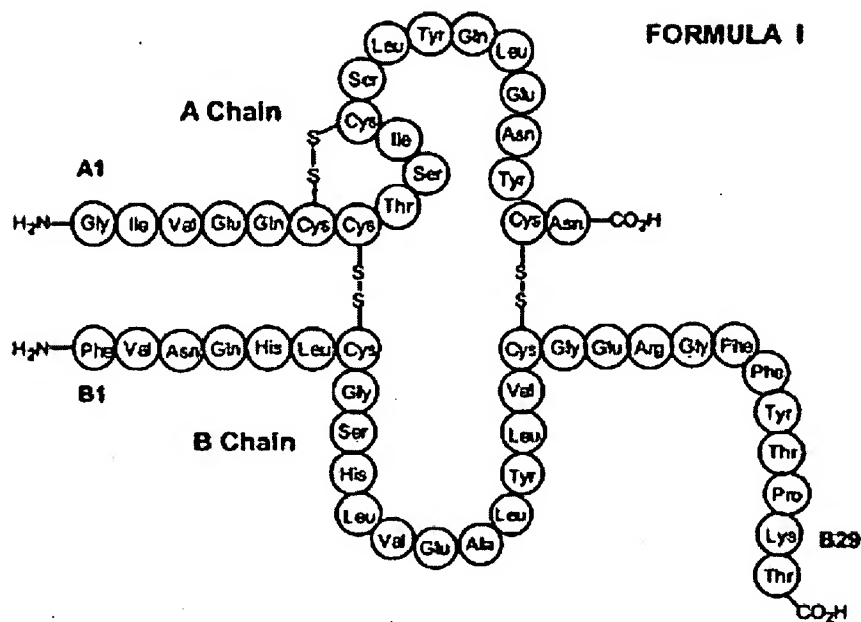
66. (Currently amended) An insulin conjugate comprising an insulin molecule, a reactive group and an albumin a blood protein, the insulin molecule comprises an A chain and a B chain and the reactive group being is a maleimido-containing group, wherein the reactive group is coupled to an available amino group of the insulin molecule selected from the α -amino groups group of the N-terminus amino acids acid of chains A and the B chain of the insulin molecule and the ϵ -amino group of Lys B29, and wherein the reactive group is covalently bonded to the albumin blood protein.

67.-68. (Cancel)

69. (Currently amended) The insulin conjugate of claim 66, wherein the available amino α -amino group is the α -amino group of Phe B1.

70. (Previously presented) The insulin conjugate of claim 66, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

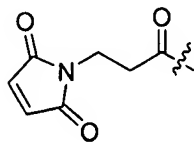
71. (Currently amended) The insulin conjugate of claim 66, wherein the insulin molecule is of formula I:



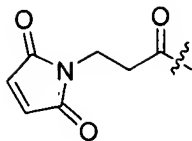
and the reactive group is coupled to the α -amino group of an amino acid of the insulin molecule at a position selected from the positions Gly A1, Phe B1 and Lys B29 of the insulin molecule.

72. (Cancel)

73. (Currently amended) The insulin conjugate of claim 66, wherein the reactive group coupled to the ~~available amino~~ α -amino group of the insulin molecule is:



74. (Currently amended) The insulin conjugate of claim 69, wherein the reactive group coupled to the ~~available amino~~ α -amino group of the insulin molecule is:



75. (Cancel)

76. (Currently amended) The insulin conjugate of claim 66, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

77. (Currently amended) The insulin conjugate of claim 69, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

78. (Currently amended) The insulin conjugate of claim 74, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule via a linker.

79. (Currently amended) The insulin conjugate of claim [[75]] 73, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

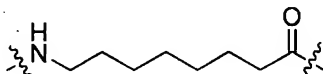
80. (Currently amended) The insulin conjugate of claim 76, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amino~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino)ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

81. (Currently amended) The insulin conjugate of claim 77, wherein the reactive group is coupled to the ~~available-amino~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amino~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino)ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

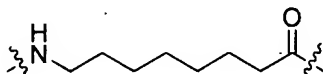
82. (Currently amended) The insulin conjugate of claim 78, wherein the reactive group is coupled to the ~~available-amine~~ α -amino group of the insulin molecule by reacting a linker with the reactive group and the ~~available-amine~~ α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy]] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

83. (Previously presented) The insulin conjugate of claim 79, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy]] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

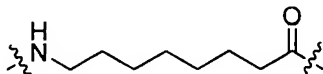
84. (Previously presented) The insulin conjugate of claim 76, wherein the linker is:



85. (Previously presented) The insulin conjugate of claim 77, wherein the linker is:



86. (Previously presented) The insulin conjugate of claim 78, wherein the linker is:



87. (Cancel)

88. (Cancel)

89. (Currently amended) The insulin conjugate of claim [[72]] 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

90. (Currently amended) The insulin conjugate of claim [[72]] 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropionylcarbonyl)aminooctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropionylcarbonyl)aminooctanamide.

91. (Cancel)

92. (Cancel)

93. (Currently amended) The insulin conjugate of claim [[92]] 66, wherein the albumin is recombinant albumin.

94.-115. (Cancel)

116. (Previously presented) A pharmaceutical composition comprising an insulin derivative of claim 38 and a pharmaceutically acceptable carrier.

117. (Currently amended) A ~~pharmaceutically acceptable carrier~~ pharmaceutical composition comprising an insulin conjugate of claim 66 and a pharmaceutically acceptable carrier.

118. (Previously presented) A method of treating a glycaemic-related disease in a subject, comprising:

administering to the subject an insulin derivative of claim 38, to thereby treat the glycaemic related disorder.

119. (Previously presented) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

120. (Previously presented) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

121. (Previously presented) A method of treating a glycaemic-related disease in a subject, comprising:

administering to the subject an insulin conjugate of claim 66, to thereby treat the glycaemic related disorder.

122. (Previously presented) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

123. (Previously presented) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

124. (Currently amended) A method of making the conjugate of claim 66 *in vivo* in a subject, the method comprising administering to a subject an insulin derivative of claim 38, wherein a covalent bond between the reactive group of the insulin derivative and the ~~blood protein~~ albumin is formed in the subject.

125.-130. (Cancel)

131. (Previously presented) The insulin derivative of claim 41, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.

132. (New) The insulin derivative of claim 38, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.